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Effects of Intraoperative Insufflation With Warmed, Humidified CO_2 during Abdominal Surgery: A Review

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Purpose: During a laparotomy, the peritoneum is exposed to the cold, dry ambient air of the operating room (20°C, 0%–5% relative humidity). The aim of this review is to determine whether the use of humidified and/or warmed CO_2 in the intraperitoneal environment during open or laparoscopic operations influences postoperative outcomes.
Methods: A review was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The PubMed, OVID MEDLINE, Cochrane Central Register of Controlled Trials and Embase databases were searched for articles published between 1980 and 2016 (October). Comparative studies on humans or nonhuman animals that involved randomized controlled trials (RCTs) or prospective cohort studies were included. Both laparotomy and laparoscopic studies were included. The primary outcomes identified were peritoneal inflammation, core body temperature, and postoperative pain.
Results: The literature search identified 37 articles for analysis, including 30 RCTs, 7 prospective cohort studies, 23 human studies, and 14 animal studies. Four studies found that compared with warmed/humidified CO_2, cold, dry CO_2 resulted in significant peritoneal injury, with greater lymphocytic infiltration, higher proinflammatory cytokine levels and peritoneal adhesion formation. Seven of 15 human RCTs reported a significantly higher core body temperature in the warmed, humidified CO_2 group than in the cold, dry CO_2 group. Seven human RCTs found lower postoperative pain with the use of humidified, warmed CO_2.
Conclusion: While evidence supporting the benefits of using humidified and warmed CO_2 can be found in the literature, a large human RCT is required to validate these findings.

Keywords: *Humidified; Carbon dioxide; Pneumoperitoneum; Surgical adhesions; Intraperitoneal inflammation*

INTRODUCTION

In recent years, minimally invasive abdominal operations have become prevalent. However, based on pathology and patient factors, open abdominal operations continue to be routinely performed. After open abdominal surgery, commonly encountered complications include postoperative ileus, postoperative infection, wound infection and anastomotic breakdown. Intraoperatively, the bowel is exposed to the ambient air, which is cold and dry relative to the unexposed abdominal environment. The average room temperature in the operating room (OR) is typically 20°C, and the average relative humidity is 0%–5%. The OR has negative air ventilation; i.e., clean air is blown in from the ceiling and then out of the OR. The dry and cold air convection causes serosal and peritoneal desiccation [1]. Desiccation results from superficial water loss through diffusion and convective gas movements. When the ambient gas is fully saturated, water loss cannot occur, regardless of the gas movements above the surface. By contrast, if the gas is not fully saturated with water, then convection will be a decisive factor for desiccation. Diffusion alone is a rather slow

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transfer process, but convection maximizes the evaporation rate by constantly exchanging the 'humidified' gas close to the surface of the intestine with 'dry' ambient gas (the diffusion gradient is maintained at a maximum) [1]. Surgeons who perform a prolonged laparotomy frequently cover the bowel with a warm, wet sponge to moisten the bowel.

Peritoneal desiccation leads to peritoneal inflammation, loss of barrier function and increased risk of infection [1-4], and peritoneal inflammation can lead to postoperative adhesion formation and long-term bowel obstruction [1, 2]. Cooling of the bowel due to exposure can lead to vasoconstriction of splanchnic blood flow to the intestine, which may increase the risk of bowel anastomosis breakdown. Bowel desiccation may also be a factor in delaying the return of bowel function. Previous studies [2-4] have also suggested that desiccation and cooling of the peritoneum from open surgical wounds or the use of cold, nonhumidified CO_2 insufflation gas may cause oxidative stress on peritoneal mesothelial cells. Thus, desiccation of the peritoneum has the potential to cause peritoneal inflammation and reduced splanchnic blood flow, with associated long-term consequences. One way of mitigating desiccation is the use of humidified, warmed CO_2 gas. CO_2 gas is heavier than other components of room air (nitrogen, oxygen) and therefore tends to sink into the abdominal wound rather than drift away. CO_2 also maintains heat, thus creating a localized greenhouse effect within the abdominal cavity. Animal studies have also suggested that CO_2 pneumoperitoneum has anti-inflammatory properties compared with a standard laparotomy, with a significantly greater increase in anti-inflammatory cytokines (interleukin [IL]-6) [5] and earlier expression of anti-inflammatory cytokines (IL-6) [6]. CO_2 pneumoperitoneum allows better regulation of the immune response to local infection (*Escherichia coli* peritonitis) and has been associated with lower levels of proinflammatory cytokines (IL-1, tumor necrosis factor-α [TNF-α]), a lower rate of positive blood culture, and lower bacterial counts in peritoneal fluid [6]. These observations may reflect a combination of improved regulation of the immune response, better splanchnic blood flow and less desiccation as a result of CO_2 pneumoperitoneum [7]. The aim of this review was to determine whether evidence supporting the benefits associated with the use of humidified, warmed CO_2 during abdominal surgery can be found in the literature.

METHODS

A comprehensive literature search and review was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [8]. Two authors (JYC, AK) performed the literature search using the databases PubMed, OVID MEDLINE, Cochrane Central Register of Controlled Trials and Embase (1980–2016 October). The key search terms included the following: "carbon dioxide," "humidified," "laparotomy," "surgical procedures, minimally invasive," "pneumoperitoneum," "laparoscopy," "temperature," "helium," "outcomes," "inflammation," and "postoperative pain."

Comparative studies, including randomized controlled trials (RCTs) and prospective cohort studies, were included. Both laparotomy and laparoscopic studies were reviewed; laparoscopic studies that compared the effects of humidified, warmed CO_2 pneumoperitoneum with those of cold, dry CO_2 pneumoperitoneum were included because cold, dry CO_2 pneumoperitoneum is analogous to and mimics the environment in the operating theatre. Studies of humans and nonhuman animals were included. For human subject studies, a sample size of at least 20 patients was a prerequisite for inclusion. For work conducted with non-human animals, a minimum of 10 animals per treatment group was considered necessary for inclusion. A lower minimum sample size was acceptable for nonhuman animal studies because such studies tend to be more homogenous and better controlled than human studies.

Potentially eligible studies were selected based on their titles and abstracts. The full texts of these publications were obtained and reviewed to confirm the eligibility of each study for inclusion in the review. The reference lists of included and excluded articles were searched to identify any additional relevant articles. All publications related to each individual RCT were obtained along with the trial protocol, if available, in electronic format. The primary outcomes identified were peritoneal inflammation, core body temperature, postoperative pain, wound infection and tumor growth. An assessment of the quality of the evidence provided in the various studies was determined for each study by using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence system [9]. Given the significant heterogeneity in the outcome measures, no formal meta-analysis was applied, and the study results are presented individually in tabular format.

RESULTS

The literature search identified 37 articles that met the inclusion criteria for analysis (Fig. 1), including 30 RCTs, 7 nonrandomized cohort studies, 23 human studies, and 14 animal studies. The animal model studies examined the effects of pneumoperitoneum under various conditions (warmed/humidified CO_2 vs. cold/dry CO_2 vs. ambient air vs. helium). In human studies, the effects of various pneumoperitoneum conditions (warmed/humidified CO_2 vs. cold/dry CO_2 vs. air) in different operative settings were examined (bariatric surgery, colorectal surgery, gynecological surgery, and hepatobiliary surgery).

Effects on peritoneal inflammation

Eight studies compared the effects of warmed, humidified CO_2 insufflation vs. cold, dry CO_2 insufflation on peritoneal morphology, inflammation and adhesion formation (Table 1). Six studies were animal-based, and 2 were human studies. The 2 human studies examined the effects in patients undergoing a laparoscopic

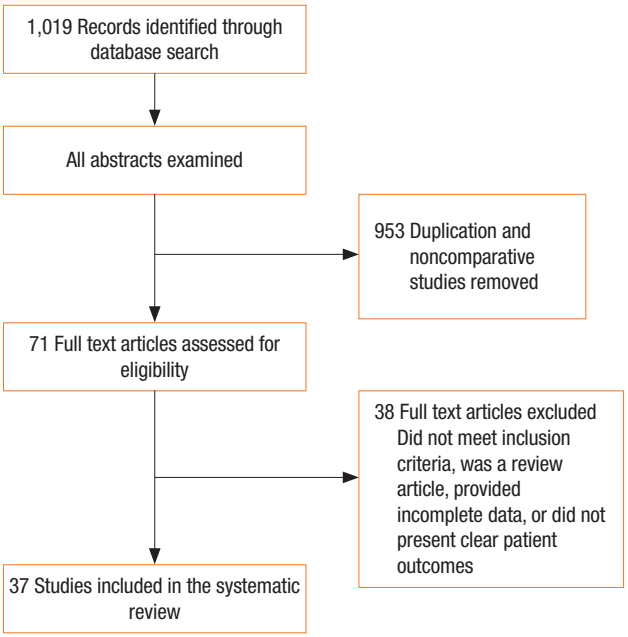

Fig. 1. Study flow chart.

cholecystectomy or a laparoscopic colectomy [10, 11]. Brokelman et al. [10] found that the peritoneal plasminogen activator inhibitor-1 (PAI-1) level was ten times higher in peritoneal biopsies of patients who received cold gas insufflation than it was in patients who received warmed, humidified CO_2. Elevated PAI-1 levels can lead to lower levels of fibrinolysis and increased fibrin deposition, resulting in increased peritoneal adhesion formation [12]. An analysis of abdominal drain fluid 20 hours postoperatively found no difference in the levels of inflammatory cytokines (IL1, 6, 8, 10, and TNF-α) between the 2 groups [11].

The largest animal study employed 150 rats. The group that received cold, dry gas pneumoperitoneum had more intense peritoneal injury, with intra-abdominal adhesions, than the group that received warmed, humidified gas pneumoperitoneum [13]. Three smaller animal studies [14-16] found no difference in peritoneal inflammation between the 2 pneumoperitoneum groups; however, one found that cold, dry gas insufflation resulted in greater infiltration of the peritoneum by lymphocytes and desquamation of the mesothelial cells, with exposure of the underlying basement membranes [17]. One animal study [18] compared the effects of CO_2 pneumoperitoneum with those of air pneumoperitoneum and found that the air pneumoperitoneum group had higher levels of infiltration of the peritoneum by inflammatory cells than the CO_2 pneumoperitoneum group, with a threefold increase in the number of polymorphoneutrophils (PMNs) and lower PMN apoptosis rates. Collectively, these studies suggest that insufflation with cold, dry gas to create the pneumoperitoneum is associated with greater peritoneal injury, increased adhesion formation and greater recruitment of inflammatory cells; however, no difference in peritoneal cytokine levels was observed between treatment groups.

Effects on core body temperature

The surface area of the peritoneal cavity is equivalent to that of the external body, 1–2 m^2 [2]. Approximately 10% of cardiac output is routed through the splanchnic system. The peritoneal cavity has the potential for extensive heat exchange and resultant morbidity due to hypothermia [19-21]. Twenty studies examined the effects of humidified, warmed CO_2 on core body temperature (Table 2). Three studies were animal-based, and 17 studies were human-based. Among the 17 available human studies, 15 were RCTs, and 2 were nonrandomized prospective studies. The total number of patients in the RCTs was 1,014. The studies all involved laparoscopic operations. Many of the studies had small sample sizes, and only 7 studies had more than 30 patients in each arm [22-28]. Seven studies [19, 23, 27, 29-32] found significantly higher core body temperatures in the treatment group (humidified, warmed CO_2 group) than in the control group (cold, dry CO_2) whereas nine studies did not find any significant difference [22, 24-26, 28, 33-36].

The largest human-based RCT involved 195 patients who had undergone a laparoscopic appendectomy [26]. The study found no difference in core body temperature between the treatment group and the control group. However, the next-largest human RCT, based on 148 patients who had undergone a laparoscopic cholecystectomy, found higher core temperatures in the warmed, humidified CO_2 group (37.07°C vs. 36.85°C, P = 0.01) [27]. Another study found that the core temperature decreased in both the treatment and the control groups; however, the decrease was greater in the treatment group (0.7°C to 0.3°C and 0.3°C to 0.1°C, respectively) [37].

The largest animal study was conducted with 150 rats [13]; a decrease in core body temperature of between 2.3°C and 3.1°C was observed in the control group treated with cold/dry CO_2 pneumoperitoneum whereas the core body temperature of the humidified/warmed CO_2 group increased by 1.3°C. Another animal study examined the effects of 4 different combinations of pneumoperitoneum conditions: cold/dry, cold/humidified, warm/dry, and warm/humidified [15]. Conditions that were either cold or dry resulted in a significant decrease in core body temperature. By contrast, warmed/humidified pneumoperitoneum resulted in an increase in core body temperature of 2.4°C (P = 0.031) [15]. Bessell et al. [38] suggested that the humidity of the insufflated CO_2 gas was more important than its temperature in maintaining core body temperature. Their study compared the use of dry-warm CO_2 with that of dry-cold CO_2 and found that both resulted in a significant drop in core body temperature. The provision of warmed, rather than cold, insufflated gas conferred no protection against changes in core temperature during laparoscopic surgery due to the small amount of heat required to warm the gas to body temperature. The study suggested that a greater amount of body

Table 1. Effects of humidified, warmed carbon dioxide on peritoneal inflammation

Study	Study type	Humans/ animals	Operation/samples taken	Device used	Study group		Control group		Results
					Treatment	No.	Treatment	No.	
Peng et al. 2009 [13]	RCT	Animals (rats)	Pneumoperitoneum creation (peritoneum/ muscle of anterior/ upper abdomen harvested)	Self-developed system	Warmed (37°C) + humidified (95% RH) CO_2 gas	75	Cold (21°C) + dry (<1% RH) CO_2 gas	75	Cold, dry group: intense peritoneal injury + intra-abdominal adhesions Warmed, humidified group: less peritoneal injury, no adhesion
Brokelman et al. 2008 [10]	RCT	Humans	Laparoscopic cholecystectomy (parietal peritoneal biopsy)	Thermoflator (Karl Storz GmbH & Co., Tuttlingen, Germany)	Warmed (37°C) CO_2 gas	15	Cold (21°C) CO_2	15	Significantly higher PAI (10×) level in the peritoneum of the control group with cold CO_2 insufflation
Sammour et al. 2010 [11]	RCT	Humans	Elective laparoscopic colectomy (4-mL peritoneal drain fluid)	Insuflow (MR 860, Fisher & Paykel Healthcare, Auckland, New Zealand)	Warmed (37°C) + humidified (98% RH) CO_2	41	Standard CO_2 (19°C, 0% RH)	41	No difference in peritoneal cytokine levels (IL1, 6, 8, 10, TNF-α)
Sammour et al. 2011 [14]	Prospective, non-RCT	Animals (rats)	Pneumoperitoneum creation (biopsies of liver, kidney, pancreas, jejunum)	Insufflator: CO_2-OP-Pneu insufflator, (Wisap, Munich, Germany) Humidifier: Insuflow (MR 860, Fisher & Paykel Healthcare)	Warmed (37°C), humidified (98% RH) CO_2	10	Standard (19°C, 0% RH)	10	No difference in oxidative stress measures (malondialdehyde-MDA, Protein CarbonI-PC)
Moehrlen et al. 2006 [18]	RCT	Animals (NMRI mice)	Pneumoperitoneum creation (peritoneal lavage sample)	Olympus laparoscopic UHI-1 insufflator (Olympus Volketswil, Volketswil, Switzerland)	CO_2	9	Air	9	CO_2 pneumoperitoneum resulted in less peritoneal inflammation Air resulted in higher PMN recruitment (3×), and lower PMN apoptosis rates
Hazebroek et al. 2002 [15]	RCT	Animals (rats)	Pneumoperitoneum creation (peritoneal tissue samples from anterior abdominal wall)	MR600 anesthesia respiratory humidifier (Fisher & Paykel Healthcare)	Group 1- Cold (24.9°C), dry (4% RH) CO_2 Group 2- Cold (24.8°C), humidified (87% RH) CO_2 Group 3- Warm (36.9°C), dry (5% RH) CO_2 Group 4- Warm (37.1°C), humidified (88% RH) CO_2	12 12 12 12	No pneumoperitoneum	12	No significant morphological difference among the groups
Erikoglu et al. 2005 [17]	RCT	Animals (rats)	Pneumoperitoneum creation (peritoneal tissue samples)	Datascope GmbH, Passport XG, Bensheim	Warmed (40°C), humidified (98% RH) CO_2 Cold (21°C), dry (2% RH) CO_2	10 10	No pneumoperitoneum	10	Greater peritoneal alteration in the cold, dry CO_2 group
Margulis et al. 2005 [16]	RCT	Animals (pigs)	Laparoscopic nephrectomy (peritoneal fluid sample)	Insuflow (MR 860, Fisher & Paykel Healthcare)	Warmed, humidified CO_2	5	Cold, dry CO_2	5	No difference in serum and peritoneal levels of TNF-α, IL-1, IL-6, glucose, and cortisol

RCT, randomized controlled trial; RH, relative humidity; TNF, tumor necrosis factor; IL, interleukin.

Table 2. Effects of warmed, humidified carbon dioxide on core body temperature

Study	Study type	Humans/ animals	Operation	Device used	Study group		Control group		Results
					Treatment	No.	Treatment	No.	
Nguyen et al. 2002 [30]	RCT	Humans	Lap Nissen fundoplication	Insuflow (MR 860, Fisher & Paykel Healthcare, Auckland, New Zealand)	Warmed (37°C) + humidified (95% RH) CO_2 gas + warming blanket	10	Warming blanket	10	Intraabdominal T increased by 0.2°C in the study group, but decreased by 0.5°C in the control group after 1.5 hours Difference not significant
Hamza et al. 2005 [29]	RCT	Humans	Lap Roux-en-Y gastric bypass	Insuflow (MR 860, Fisher & Paykel Healthcare, NZ)	Warmed (37°C) + humidified (95% RH) CO_2 gas	23	Room temperature (20°C) gas	21	Study group showed a significantly higher core body temperature intraoperatively (35.5°C vs. 35.0°C) and at the end of surgery, P = 0.01 Study group also had a significantly lower rate of postoperative shivering (0% vs. 19%)
Davis et al. 2006 [22]	RCT	Humans	Lap Roux-en-Y gastric bypass	Control- standard CO_2 Group 1- heated insufflator tube set (Stryker) Group 2,3- Insuflow (MR 860, Fisher & Paykel Healthcare)	Group 1- Warmed CO_2 Group 2- Humidified CO_2 Group 3- Warmed + Humidified CO_2	33 (11 each group)	Standard CO_2	11	No difference in core body temperature or humidity
Peng et al. 2009 [13]	RCT	Animals (rats)	Laparoscopic insufflation only	Self-developed system	Warmed (37°C) + humidified (95% RH) CO_2 gas	75	Cold (21°C) + dry (<1% RH) CO_2 gas	75	Significant decrease in core body temperature in cold, dry CO_2 group (decrease of 2.3°C–3.11°C); warmed + humidified CO_2 group showed increased temperature by 1.3°C
Mouton et al. 1999 [33]	RCT	Humans	Elective laparoscopic cholecystectomy	Modified LINS-1000 Insufflator (Cook Medical Technology, Queensland, Australia)	Warmed (37°C) + humidified (90% RH) CO_2	20	Standard CO_2 (21°C, 0% RH)	20	No difference in core body temperature or humidity
Farley et al. 2004 [23]	RCT	Humans	Elective laparoscopic cholecystectomy	Insuflow Filter Heater Hydrator; (Lexion Medical, St Paul, MN, USA)	Warmed (35°C), humidified (95% RH) CO_2	49	Standard CO_2	52	Core body temperature increased by 0.29°C in humidified, warmed CO_2 group and decreased by 0.03°C in standard group, P = 0.01
Saad et al. 2000 [34]	RCT	Humans	Elective laparoscopic cholecystectomy	Flow Therme (WISAP, Sauerlach, Germany)	Warmed (37°C) CO_2	10	Standard (21°C) CO_2	10	No difference in core body temperature
Bäcklund et al. 1998 [31]	RCT	Humans	Elective laparoscopic surgery (not specified)	Therme-Pneu Electronic Ltd., Wisap, Germany	Warmed (37°C) CO_2	13	Cold (21°C) CO_2	13	Warm CO_2 group had higher core body temperature (35.8°C vs. 35.4°C, P < 0.05) Warm CO_2 group had higher cardiac index intraoperatively (P < 0.05). Warm CO_2 group had better urine output (P < 0.05) and lower requirement of mannitol intraoperatively for low urine output

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Table 2. Continued

Study	Study type	Humans/ animals	Operation	Device used	Study group		Control group		Results
					Treatment	No.	Treatment	No.	
Nelskylä et al. 1999 [37]	RCT	Humans	Laparoscopic hysterectomy	Thermoflator (Karl Storz, Tuttlingen, Germany)	Warmed (37°C) CO_2	18	Cold (24°C) CO_2	19	Greater decrease in temperature in the group with warmed CO_2 (0.7°C vs. 0.3°C, 0.3°C vs. 0.1°C)
Ozgonul et al. 2007 [24]	RCT	Humans	Elective laparoscopic cholecystectomy	H-500 Fluid warmer (Level 1 Technologies, Inc., Rockland, MA, USA)	Warmed (37°C) CO_2	31	Cold (21°C) CO_2	31	No difference in core body temperature, mean arterial pressure, or heart rate
Hazebroek et al. 2002 [15]	RCT	Animals (rats)	Pneumoperitoneum creation	MR600 anesthesia respiratory humidifier (Fisher & Paykel Healthcare)	Group 1- Cold (24.9°C) dry (4% RH) CO_2 Group 2- Cold (24.8°C), humidified (87% RH) CO_2 Group 3- Warm (36.9°C), dry (5% RH) CO_2 Group 4- Warm (37.1°C), humidified (88% RH) CO_2	12 12 12 12	No pneumoperitoneum	12	Cold, dry CO_2 group: decrease in core body temperature by 1.6°C ($P < 0.001$) Cold, humidified CO_2 group: decrease in core body temperature by 0.3°C ($P = 0.011$) Warm, dry CO_2 group: decrease in core body temperature by 0.9°C ($P = 0.031$) Warm, humidified CO_2 group: increase in core body temperature by 2.4°C ($P = 0.031$)
Ott 1991 [19]	Prospective, non-RCT	Humans	Diagnostic laparoscopy	R. Wolf/Weiss insufflator	Warmed (35°C) CO_2	20	Cold CO_2	20	In the cold CO_2 group, a decrease in core body temperature of 0.3°C per 50 L of CO_2 used was observed Warmed, humidified group had improved intraoperative normothermia and postoperative pain, and reduced recovery room stay
Bessell et al. 1995 [38]	RCT	Animals (pigs)	Pneumoperitoneum creation	LINS-1000 insufflator (Cook Medical Technology, Queensland, Australia)	Warmed (30°C) CO_2	6	Cold (25°C) CO_2	6	No significant temperature difference was observed between animals receiving cold CO_2 and those receiving warm CO_2 over a 3-hour period
Yeh et al. 2007 [35]	Prospective, non-RCT	Humans	Laparoscopic colectomies	Insuflow (MR 860, Fisher & Paykel Healthcare)	Warmed (36°C), humidified (95% RH) CO_2	20	Cold (30.2°C), dry (0% RH)	20	No significant difference in change in core body temperature
Manwaring et al. 2008 [25]	RCT	Humans	Laparoscopic gynecologic procedures	Insuflow (MR 860, Fisher & Paykel Health care)	Warmed (37°C), humidified (100% RH) CO_2	30	Cold, dry CO_2	30	No difference in core body temperature or recovery room time
Champion and Williams 2006 [36]	RCT	Humans	Laparoscopic Roux-en-Y gastric bypass	Insuflow device (Lexion Medical, St Paul, MN, USA)	Warmed (35°C), humidified (95% RH) CO_2	25	Cold, dry CO_2	25	No difference in core body temperature, operative time, or recovery room time

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Table 2. Continued

Study	Study type	Humans/ animals	Operation	Device used	Study group		Control group		Results
					Treatment	No.	Treatment	No.	
Yu et al. 2013 [26]	RCT	Humans	Laparoscopic appendectomy	Insuflow (MR 860, Fisher & Paykel Healthcare)	Warmed (37°C), humidified (98% RH) CO_2	97	Cold (20°C–21°C), dry (0% RH) CO_2	98	No difference in core body temperature
Savel et al. 2005 [32]	RCT	Humans	Laparoscopic Roux-en-Y gastric bypass	Insuflow device (Lexion Medical, St. Paul, MN, USA)	Warmed (35°C), humidified (95% RH) CO_2	15	Cold, dry CO_2	15	No change in core body temperature in the cold, dry CO_2 group In the humidified, warmed CO_2 group, core body temperature increased from 35.8°C to 36.2°C (P = 0.004)
Klugsberger et al. 2014 [27]	RCT	Humans	Laparoscopic cholecystectomy	Optitherm device (Storz, Tuttlingen, Germany)	Warmed, humidified CO_2	81	Cold, dry CO_2	67	Higher core body temperature in the warmed, humidified CO_2 group (37.07°C vs. 36.85°C, P = 0.01)
Herrmann and De Wilde 2015 [28]	RCT	Humans	Laparoscopic assisted vaginal hysterectomy	Insuflow (MR 860, Fisher & Paykel Healthcare)	Warmed (37°C), humidified (98% RH) CO_2	48	Cold (20°C–21°C), dry (0% RH) CO_2	49	No difference in core body temperature

RCT, randomized controlled trial; RH, relative humidity.

heat is required to saturate the insufflated gas. Most of the hypothermic effect they observed was due to this saturation and could be minimized by humidifying the gas.

While some evidence exists that warmed, humidified CO_2 results in better control of core body temperature than cold, dry CO_2, this outcome has not been shown universally. Overall, the effect on core temperature appears to be more pronounced in larger studies than in smaller studies, suggesting that the smaller-scale studies were underpowered.

Effect on postoperative pain

Sixteen studies compared the effects of humidified, warmed CO_2 with those of cold, dry CO_2 on postoperative pain (Table 3). All of these studies were human RCTs, with a total of 1,223 patients. Pain was measured using a combination of the visual analogue score (VAS), verbal rating scale (VRS), morphine equivalent daily dose (MEDD), analogue pain score, Likert Scale and total analgesia requirement. Nine studies (with a total of 602 patients) found no difference in postoperative pain [11, 22, 23, 25, 26, 30, 32, 34, 36] whereas seven studies (with a combined total of 621 patients) found that pain was significantly lower with the use of humidified, warmed CO_2 [27-29, 33, 39-41].

The largest RCT, which was conducted by Yu et al. [26], revealed no difference in MEDD and VAS scores between the warmed, humidified CO_2 pneumoperitoneum group and the cold, dry CO_2 pneumoperitoneum group among patients who had undergone a laparoscopic appendectomy. However, a laparoscopic appendectomy is a minor operation, and whether the results of such a study can be justifiably compared with those of other studies involving major surgeries is questionable. The next-largest human RCT, which included 148 patients who had undergone a laparoscopic cholecystectomy, found that postoperative pain measured by using the VAS at day 0 was significantly lower in the warmed, humidified CO_2 group than it was in the cold, dry CO_2 group [27].

Similarly, Mouton et al. [33] determined that warmed, humidified CO_2 resulted in less perioperative pain, with improved pain noted for up to 10 days postoperatively, and Farley et al. [23] observed a similar benefit at postoperative day 14. Thus, while some evidence showing that the use of warmed, humidified CO_2 reduces postoperative pain exists, the overall evidence is inconclusive.

Effect on respiratory function

The CO_2 in the peritoneal cavity may be absorbed systemically, with conversion to carbonic acid (H_2CO_3) (Table 4). This buffering effect may decrease pH both locally (within the peritoneum) and systemically depending on the intrinsic carbonic acid levels. Consistent with this possibility, an animal study by Bergström et al. [42] found that CO_2 pneumoperitoneum resulted in a locoregional decrease in pH (6.4 vs. 7.5, P = 0.001) and a decrease in systemic arterial pH (7.43 vs. 7.49, P = 0.004) compared with insufflation with another gas (helium). Another independent animal study found that increasing the CO_2 temperature resulted in a greater systemic arterial concentration of CO_2 and a corre-

Table 3. Effects of warmed, humidified carbon dioxide on postoperative pain in humans

Study	Study type	Humans/ animals	Operation	Device used	Study group		Control group		Results	Method of measuring pain
					Treatment	No.	Treatment	No.		
Nguyen et al. 2002 [30]	RCT	Humans	Lap Nissen fundoplication	Insuflow device (Lexion Medical, St. Paul, MN, USA)	Heated + humidified CO_2 gas + warming blanket	10	Warming blanket	10	No significant difference	VAS
Hamza et al. 2005 [29]	RCT	Humans	Lap Roux-en-Y gastric bypass	Insuflow device (Lexion Medical)	Heated + humidified CO_2 gas	23	Room temperature gas	21	Maximum VRS and morphine consumption significantly lower in study group	11-point VRS
Davis et al. 2006 [22]	RCT	Humans	Lap Roux-en-Y gastric bypass	Control- standard CO_2 Group 1- heated insufflator tube set (Stryker) Group 2,3- Insuflow (MR 860, Fisher & Paykel Healthcare, Auckland, New Zealand)	Group 1- heated CO_2 Group 2- humidified CO_2 Group 3- heated+ humidified CO_2	33 (11 each group)	Standard CO_2	11	No difference in postoperative pain	VAS
Sammour et al. 2010 [11]	RCT	Humans	Elective laparoscopic colonic resections	Insuflow (MR 860, Fisher & Paykel Healthcare)	Warmed (37°C) + humidified (98% RH) CO_2	41	Standard CO_2 (19°C, 0% RH)	41	No difference in postoperative pain	(1) VAS (2) MEDD
Mouton et al. 1999 [33]	RCT	Humans	Elective laparoscopic cholecystectomy	Modified LINS-1000 Insufflator (Cook Medical Technology, Queensland, Australia)	Warmed (37°C) + humidified (90% RH) CO_2	20	Standard CO_2 (21°C, 0% RH)	20	Humidified + warmed CO_2 group had significantly less postoperative pain at 6 hours, at 1st, 2nd, 3rd day postoperatively and on follow-up on day 10 Mean time to return to normal activity was significantly lower in warmed, humidified group (5.9 days vs. 10.9 days)	Analogue pain score
Farley et al. 2004 [23]	RCT	Humans	Elective laparoscopic cholecystectomy	Insuflow device (Lexion Medical)	Warmed (35°C), humidified (95% RH) CO_2	49	Standard CO_2	52	No difference in postoperative pain during admission However, significant difference in pain on follow-up at week 2 (Likert Scale 1.0 vs. 0.3, P = 0.02)	(1) Likert Scale (0–10) (2) Morphine Equivalent Score (use of analgesia)
Saad et al. 2000 [34]	RCT	Humans	Elective laparoscopic cholecystectomy	Flow Therme, (WISAP, Sauerlach, Germany)	Warmed (37°C) CO_2	10	Standard (21°C) CO_2	10	No difference in postop pain (visual analogue score + analgesia usage)	(1) VAS (2) Postoperative ibuprofen usage
Beste et al. 2006 [39]	RCT	Humans	Laparoscopic gynecological procedures: tubal ligation, salpingo-oophorectomy, cystectomy, ablation of endometriosis, adhesiolysis, chemopertubation	Insuflow device (Lexion Medical)	Warmed, humidified CO_2	47	Warmed, dry CO_2	42	Humidified CO_2 reduced postoperative pain and requirements for analgesia	Total morphine equivalent

(*Continued to the next page*)

Table 3. Continued

Study	Study type	Humans/ animals	Operation	Device used	Study group		Control group		Results	Method of measuring pain
					Treatment	No.	Treatment	No.		
Kissler et al. 2004 [40]	RCT	Humans	Laparoscopic gynecological procedures	Laparo-CO_2-pneu 2232 (Wolf, Knittlingen, Germany)	Warmed, humidified CO_2 Warmed, dry CO_2	30 30	Cold, dry CO_2	- 30	Significant differences in postoperative pain and analgesia requirements Non-significant tendency towards less pain and higher patient satisfaction in patients who received cold, dry CO_2	(1) Total analgesia requirement (2) VAS (3) Patient satisfaction
Manwaring et al. 2008 [25]	RCT	Humans	Laparoscopic gynecological procedures	Insuflow (MR 860, Fisher & Paykel Healthcare)	Heated (37°C), humidified (100% RH) CO_2	30	Cold, dry CO_2	30	No difference in postoperative pain or analgesia requirements	VAS
Champion and Williams 2006 [36]	RCT	Humans	Laparoscopic Roux-en-Y gastric bypass	Insuflow device (Lexion Medical)	Heated (35°C), humidified (95% RH) CO_2	25	Cold, dry CO_2	25	No difference in analgesia requirement or abdominal pain; significant difference in shoulder pain at 18 hours (but not at 6, 12, 24, or 48 hours)	VAS
Yu et al. 2013 [26]	RCT	Humans	Laparoscopic appendectomy	Insuflow (MR 860, Fisher & Paykel Healthcare)	Heated (37°C), humidified (98% RH) CO_2	97	Cold (20-21°C), dry (0% RH) CO_2	98	No difference in quantity of analgesia required No difference in pain on visual analogue score	(1) MEDD (2) VAS
Savel et al. 2005 [32]	RCT	Humans	Laparoscopic Roux-en-Y gastric bypass	Insuflow device (Lexion Medical)	Heated (35°C), humidified (95% RH) CO_2	15	Cold, dry CO_2	15	No difference in quantity of morphine required postoperatively No difference in visual analogue score	(1) Total morphine use (2) VAS
Klugsberger et al. 2014 [27]	RCT	Humans	Laparoscopic cholecystectomy	Optitherm device (Storz, Tuttlingen, Germany)	Heated, humidified CO_2	81	Cold, dry CO_2	67	Lower visual analogue score in the heated, humidified CO_2 group at postoperative day 0 No difference in total analgesia required	(1) Total analgesia requirement (2) VAS
Herrmann and De Wilde 2015 [28]	RCT	Humans	Laparoscopic assisted vaginal hysterectomy	Insuflow (MR 860, Fisher & Paykel Healthcare)	Heated (37°C), humidified (98% RH) CO_2	48	Cold (20-21°C), dry (0% RH) CO_2	49	Lower total morphine consumption in warmed, humidified CO_2 group ($P = 0.02$)	(1) Total morphine consumption (2) VAS
Benavides et al. 2009 [41]	RCT	Humans	Laparoscopic gastric banding	Insuflow device (Lexion Medical)	Heated (35°C), humidified (95% RH) CO_2	38	Cold, dry CO_2 Heated, dry CO_2	35 40	Significantly less postoperative pain in warmed, humidified CO_2 group than in the cold, dry CO_2 and heated, dry CO_2 groups ($P < 0.01$, $P < 0.05$)	MEDD

RCT, randomized controlled trial; RH, relative humidity; VAS, visual analogue score; MEDD, morphine equivalent daily dose; VRS, verbal rating scale.

sponding decrease in pH [43]. A locoregional decrease in pH and an increase in $PaCO_2$ will lead to local vasodilatation, which would be especially beneficial during bowel anastomosis.

A human study by Ozgonul et al. [24] found no difference in arterial pH, $PaCO_2$ level, or HCO_3^- level between subjects receiving cold CO_2 and those receiving warmed CO_2. Another human study [44] found that the results of a pulmonary function test at 12 hours were significantly better in the warmed CO_2 group than in the cold CO_2 group.

Other suggested effects of humidified, warmed CO_2 on the peritoneum

Although not included in the review, other interesting effects of humidified, warmed CO_2 have been discussed in the literature.

Table 4. Effects of warmed, humidified carbon dioxide on respiratory function

Study	Study type	Humans/ animals	Operation	Device used	Study group		Control group		Results
					Treatment	No.	Treatment	No.	
Bashirov et al. 2007 [43]	Prospective, non-RCT	Animals (pigs)	Pneumoperitoneum creation	Model Ref L-70 NI Hotline (Sims-Smith Industries Medical Systems, Rockland, MA, USA)	Warmed CO_2 groups	6 (7°C), 6 (22°C), 6 (37°C)	No CO_2 pneumoperitoneum	6	Increase in temperature of CO_2 resulted in increased peritoneal CO_2 absorption, increased $PaCO_2$ and a greater decrease in pH (7.44 vs. 7.26)
Uzunkoy et al. 2006 [44]	RCT	Humans	Elective lap cholecystectomy	H-500 fluid warmer (Level 1 Technologies, Inc.,Rockland, MA, USA)	Warmed CO_2 (37°C)	15	Cold CO_2 (21°C)	15	Pulmonary function test performed 12 hours after the operation found lung function was significantly better in those receiving warmed CO_2 (FVC, FEV_1, PEF)
Bergström et al. 2008 [42]	Prospective, non-RCT	Animals (pigs)	Pneumoperitoneum creation	Laparoscopic insufflator (Storz, Tuttlingen, Germany)	CO_2	10	Helium	10	CO_2 pneumoperitoneum resulted in significantly lower peritoneal pH (6.4 vs. 7.5, P = 0.001) However, very minimal changes in arterial pH (7.43 vs. 7.49, P = 0.004) were found, with no clinical significance
Ozgonul et al. 2007 [24]	RCT	Humans	Elective laparoscopic cholecystectomy	H-500 fluid warmer (Level 1 Technologies, Inc., MA, USA)	Warmed (37°C) CO_2	31	Cold (21°C) CO_2	31	No significant difference in arterial pH, pCO_2, or HCO_3^-

RCT, randomized controlled trial; RH, relative humidity; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow.

These effects were not included in this review because they were either observed in noncomparative studies or *in vitro*. However, the results of these studies are fascinating and should be mentioned.

First is the effect of humidified, warmed CO_2 on tumor migration. Nduka et al. [45] compared the effects of warmed CO_2 vs. cold CO_2 insufflation on peritoneal tumor growth. Twenty WAG rats were subjected to either cold CO_2 or warm CO_2 peritoneal insufflation. The rats then received injections of 1×10^5/mL of CC531 colon cancer cells into the peritoneal cavity. After three weeks, the extent of tumor spread and cancer weight were measured, as determined by using the peritoneal cancer index (PCI). Cold CO_2 insufflation was associated with a significantly higher PCI score (266) compared with warm CO_2 insufflation (151), indicating a greater rate of peritoneal tumor growth and spread in the cold CO_2 group (P = 0.025). This study suggested a potential pathophysiological mechanism: peritoneal trauma resulting from cold gas insufflation may be responsible for the greater rate of tumor spread.

Furthermore, Texler et al. [46] examined the spread of tumor cells in warmed, humidified CO_2 and cold, dry CO_2 environments *in vitro*. A total of 24 tumor cell cultures were insufflated with CO_2 in an airtight environment, and laparoscopic instruments were used to agitate the contents of the bottle. The study found that the use of heated and humidified CO_2 with airtight seals around the trocars *in vitro* (thus mimicking the *in vivo* laparoscopic intra-abdominal environment) reduced cell deposition on the trocars compared with cold, dry CO_2 (P = 0.015). Although not a RCT, a study by Tan [47] found that CO_2 pneumoperitoneum inhibited tumor cell growth (TCC) for the first 48 hours in rat models. At high CO_2 concentrations (10%–15%), the TCC apoptosis and necrosis rates were 2.8–5.6 times higher than those in the controls without CO_2 pneumoperitoneum (P < 0.01).

Second is the effect of warmed, humidified CO_2 on local tissue oxygen tension. A 2015 study [48] using 15 Wistar rats found that compared with ambient air, local instillation of humidified, warmed CO_2 during a laparotomy significantly increased the local tissue oxygen tension by 96.6% (29.8 mmHg) and the local tissue temperature by 3.0°C.

Third is the effect of warmed, humidified CO_2 on wound infection. Suggestions have been made that warmed, humidified carbon dioxide on open laparotomy may lead to reductions in both wound infection and intra-abdominal infections because CO_2 is bacteriostatic. For many years, CO_2 at high concentrations has

been used in modified atmosphere packaging to prolong the shelf life of fresh food. The effect of CO_2 is especially marked in fresh meat [49]. High concentrations of CO_2 have a growth-inhibiting effect on most bacteria, including both aerobes and anaerobes [50, 51]. The inhibitory effect of CO_2 is associated with two main mechanisms: suffocation and a CO_2-specific effect that acts directly on the bacterial cell [1]. A study by Persson et al. [52] found that at body temperature, the bacterial growth after 4 hours of CO_2 exposure was 1/100 that after exposure to air.

Moreover, the use of laminar ultraclean airflow from the ceiling downward to the operating table may actually help convey airborne particles from the surgeons into the operating field. A study [53] found that when a surgeon leans over a wound with such an airflow (which is common), the surgeon increases the risk of airborne wound contamination by 27 fold. Additionally, more than 90% of contaminating bacteria in clean surgical wounds have been found to originate from ambient air [54], and a substantial proportion of these bacteria contaminate the wound directly. CO_2 is heavier than air and will therefore sink to the bottom of the laparotomy wound. Surplus CO_2 from ongoing insufflation will overflow, and this convective current may help block airborne contamination, as theoretically supported by Stokes' law, which describes the settling velocity of particles in a gas/liquid. A study [6] in which 10 L/min of CO_2 was insufflated into open cardiothoracic wounds found that the rate of direct airborne contamination was reduced by 80%.

Furthermore, the use of CO_2 has been found to be beneficial in septicemia. A study by Hanly et al. [55] examined the effect of CO_2 pneumoperitoneum on lipopolysaccharide (LPS) septicemia. Two experiments were performed. The first involved randomizing 143 rats to receive either CO_2, helium, or air pneumoperitoneum while the control group did not receive pneumoperitoneum. The rats then received an IV injection of endotoxins (LPS). Survival was dramatically higher in the group receiving CO_2 insufflation (survival rate, 78%) compared with the groups receiving helium (52%) and air (55%) and compared with the control group (42%), $P < 0.05$. In the second experiment, 65 rats were administered CO_2, helium, or air pneumoperitoneum, and the control group did not receive pneumoperitoneum. All rats underwent a laparotomy, and endotoxins (LPS) were injected intraperitoneally. The survival rate was significantly higher in the CO_2 pneumoperitoneum group (85%) than that in the controls (25%), $P < 0.05$. Cytokine measurements revealed that the IL-10 level was 35% higher in the CO_2 pneumoperitoneum group than in the other groups ($P < 0.05$), and that the TNF-α level was 1 of 3 that of the other groups ($P < 0.05$). This study suggested the presence of direct humoral mediation by CO_2, in which the suppression of TNF-α release from macrophages by IL-10 may have been responsible for the increased survival. The results of this study are astounding. The possibility that CO_2 pneumoperitoneum has a positive impact on survival in septic patients implies that CO_2 pneumoperitoneum may actually be beneficial in acutely ill patients with septicemia (e.g., acute abdomen or trauma). In acute settings where laparotomies are performed more frequently, CO_2 pneumoperitoneum may still be established and may improve patient survival. This will be discussed further in the sections below.

DISCUSSION

In this literature review, human and nonhuman animal studies, as well as laparoscopic and laparotomy studies, were examined. Equivocal evidence exists concerning the benefits of warmed, humidified CO_2 on the postoperative outcomes of abdominal surgery. Four of eight studies showed that peritoneal inflammation and peritoneal damage were lower in the warmed, humidified CO_2 group than in the cold, dry CO_2 group. Some evidence also exists that warmed, humidified CO_2 results in a more desirable core body temperature (7 of 15 human RCTs) and less postoperative pain (7 of 16 human RCTs). Warmed, humidified CO_2 may lead to better postoperative lung function. Studies have found that CO_2 pneumoperitoneum leads to a decrease in local peritoneal pH. This decrease, in combination with local warming and the effects of CO_2, may lead to vasodilation in splanchnic blood flow. The locally increased splanchnic blood flow will be of benefit for the integrity of colorectal anastomosis.

This study does have several limitations. First, the studies in this review are very heterogeneous. A Cochrane review in 2011 [56] based on 16 human studies found no evidence to support the use of warmed, humidified CO_2 gas, with no observed difference in core body temperature, postoperative pain or perioperative outcomes. In 2016, a meta-analysis based on 17 laparoscopic human studies found that the only benefit of warmed, humidified CO_2 was a reduction in immediate postoperative pain [57]. In our review, we expanded our scope to include both open/laparoscopic and human/animal studies, as we believe that many of the potential benefits of warmed, humidified CO_2 would not otherwise be mentioned; one of these key benefits may be the effect on peritoneal inflammation. Second, potentially eligible studies were identified based on their title and abstracts. During the process, the two authors performing the search were blinded to neither the names of the authors nor the titles of the journals, which could contribute to selection bias.

In conclusion, the ultimate benefit of using warmed, humidified carbon dioxide during abdominal surgery remains to be determined. A need clearly exists for RCTs involving human subjects to examine the potential impacts of the use of warmed, humidified carbon dioxide during abdominal surgery on peritoneal inflammation and adhesion formation.

CONFLICT OF INTEREST

No conflicts of interest are reported.

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